REMARKS

Claims 1, 3-5, 10, 12-13 and 16-23 are pending in the application and are under examination. Claims 2, 6-9, 11 and 14-15 have been canceled. Claim 1 has been amended herein to incorporate the limitations of dependent claims 2 and 11, and claim 22 has been amended in a manner analogous to the amendment to claim 1. Support for the amendments to claims 1 and 22 is found throughout the application-as-filed, including at page 5, lines 6. The claims were amended for the purpose of accelerating prosecution and not for reasons related to patentability.

In the Office Action, claims 22 and 23 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Claims 22 and 23 were also rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not enabled because a disclosure assertedly cannot teach one to make or use something that has not been described. Claims 1-5, 10-12 and 16-23 were also rejected under 35 U.S.C. § 112, first paragraph, for assertedly lacking enablement commensurate in scope to the claims. Finally, claim 13 was subject to objection as being dependent upon a rejected base claim, although the Examiner acknowledged that it would be allowable if rewritten in independent form, including all of the limitations of the base claim and any intervening claims.

Claim Rejection – 35 U.S.C. § 112, First Paragraph (Written Description)

The Examiner rejected claims 22 and 23 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner further asserted that this was a new matter rejection, citing 37 C.F.R. § 1.118(a) as well as M.P.E.P. §§ 2163.02 and 2163.06. Specifically, the Examiner asserted that claims 22 and 23 encompass a method for treating a patient with a radiation-resistant cancer by administering a therapeutically effective amount of a HSV comprising a modification of an inverted repeat region such that only one $\gamma_1$34.5 gene expresses an active gene product. The Examiner characterizes the claims as encompassing the treatment of any type of cancer that is radiation-resistant and using any HSV that comprises a modification of an inverted repeat region such that only one $\gamma_1$34.5 gene expresses an active gene product. The Examiner asserts that the

specification does not support the entire claim scope. In response, Applicants respectfully traverse.

The Examiner has not met his burden of establishing a *prima facie* basis for rejection. According to M.P.E.P. § 2163.04 I(b), the Examiner can:

> [e]stablish a prima facie case by providing reasons why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed.

At page 10, lines 25-29 of the application-as-filed, it is stated that:

> These results demonstrate for the first time dramatic antitumor efficacy of R7020 in the treatment of experimental human tumors frequently resistant to common cancer treatments and suggest that, while R7020 is an effective antitumor agent by itself, combining irradiation with R7020 also provides more rapid and complete tumor cell destruction.

Nothing in this passage limits the invention to SQ-206 cells. In fact, the passage broadly describes the claimed subject matter as being directed to the treatment of experimental human tumors that are often resistant to common cancer treatment.

At page 10, lines 7-9, the specification also recites:

> To determine whether irradiation of the radiation-resistant SQ-206 cell lines enhanced the oncolytic effect of R7020, xenografts were infected as described above and subjected to a fractionated irradiation protocol as described below.

Thus, Applicants disclosed in the application-as-filed an embodiment of the subject matter of claims 22 and 23 in the form of modified HSV treatment of radiation-resistant tumors, *i.e.*, SQ-206 xenografts. One of ordinary skill in the art would not understand Applicants to be limiting their description to the treatment of SQ-206 tumors. Rather, one of ordinary skill would understand the disclosure as exemplifying the use of modified HSV to treat radiation-resistant tumors in describing the treatment of SQ-206 xenografts. To read the passage as narrowly demonstrating possession of a method of treating SQ-206 tumors would impermissibly render as meaningless verbiage the recitation of

"radiation-resistant" in the passage. By analogy, such an interpretation would be like reciting "epidermal" SQ-206 cells, or like reciting any number of other inherent characteristics of SQ-206 cells. The characteristic of being "radiation-resistant" would be unnecessary if the written description were confined to the treatment of SQ-206 cells. One of skill would recognize that applicant would simply recite "SQ-206 tumors" if all that was being communicated was the treatment of "radiation-resistant SQ-206 tumors" and no others.

Further, the disclosure does not indicate that the modified HSVs have a distinct effect on the radiation-resistant tumors of SQ-206 cells, and one of skill would not understand the exemplification of treatment of a radiation-resistant tumor to be a disclosure limited to the exemplified treatment without a unique effect of the modified HSVs on the SQ-206 tumors being identified. One of skill would instead interpret the exemplification of SQ-206 tumor treatment in the context of the whole disclosure of the application-as-filed, including the disclosure of using the modified HSVs to treat radiation-resistant tumors.

Applicants also disagree with the Examiner's conclusory and subjective statement that the claims are broadly drawn to the treatment of all radiation-resistant tumors. Applicants disclosed, and exemplified, the use of modified HSVs to treat a particular type of tumor, *i.e.*, a radiation-resistant tumor. Claims 22 and 23 are precisely tailored to this contribution to the art. With respect to written description, the Examiner bears the burden of establishing a *prima facie* case, for example by providing scientific reasons in support of a position that the disclosure of using modified HSVs to treat radiation-resistant tumors, as exemplified by so treating SQ-206 tumor xenografts, does not provide written descriptive support sufficient for one of skill to understand that Applicants possessed a method of using modified HSVs to treat radiation-resistant tumors. The Examiner has not established such a *prima facie* case. Accordingly, the rejection of claims 22 and 23 under 35 U.S.C. § 112, first paragraph, for asserted lack of written description has been overcome and should be withdrawn.

Moreover, the Examiner's support for the rejection is also flawed in asserting that rejected claims 22 and 23 are broad in reciting any HSV with a modified inverted repeat and any radiation-resistant cancer. Claim 23 depends from claim 22 and claim 22 defines the modified HSV using a verbatim duplication of the definition of the modified HSV contained

in the application-as-filed. The Examiner's statement is conclusory and couched in a subjective term of degree (claim breadth). With respect to "radiation-resistant" cancer, an express recitation of such a cancer is provided at page 10, lines 7-9. This disclosure provides written descriptive support for the treatment of radiation-resistant cancers.

Finally, Applicants submit that the Examiner's reliance on 37 C.F.R. § 1.118(a) is misplaced, insofar as that Rule number is presently reserved. Applicants believe that the Examiner intended to cite 37 C.F.R. § 1.121(f), as it contains language similar to the quote utilized by the Examiner. Applicants submit that this rule prohibits the introduction of new matter into the disclosure, not the claims. Amended claims do not form part of the disclosure.

For the foregoing reasons, Applicants submit that the rejection of claims 22 and 23 under 35 U.S.C. § 112, second paragraph for asserted lack of written description has been overcome and should be withdrawn.

Claim Rejection – 35 U.S.C. § 112, First Paragraph (Enablement)

The Examiner rejected claims 22 and 23 under 35 U.S.C. § 112, first paragraph, as lacking enablement based on the position that a disclosure cannot teach one to make or use something that has not been described. Applicants respectfully traverse.

The written description and enablement requirements are distinct and Applicants assert that the Examiner's position is legally erroneous. Failure to provide an adequate written description does not compel a conclusion that enablement is lacking. A specification can enable without describing. *See In re DiLeone*, 436 F.2d 1404 (C.C.P.A. 1971), which stated:

> In recent cases we have recognized that the statutory requirement that the specification "describe the invention" might not be met even where the specification satisfies the related statutory requirement that it "enable any person skilled in the art * * * to make and use the same."

This principle of patent law was recently confirmed in *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916 (Fed. Cir. 2004), which stated:

> an invention may be enabled even though it has not been described. See, e.g., In re DiLeone 58 C.C.P.A. 925, 436 F.2d 1404, 1405 (CCPA 1971) ("[I]t is possible for a specification to *enable* the practice of an invention as broadly as it is claimed, and still not describe the invention.").

The Examiner has therefore erred as a matter of law in basing the rejection on the proposition that one cannot teach how to make or use what one has not described. As a result, a *prima facie* basis for rejecting claims 22 and 23 under 35 U.S.C. § 112, first paragraph, for asserted lack of written descriptive support has not been established and the rejection should be withdrawn.

Claim Rejection – 35 U.S.C. § 112, First Paragraph (Enablement)

The Examiner rejected claims 1-5, 10-12 and 16-23 under 35 U.S.C. § 112, first paragraph, for assertedly not enabling the full scope of the claims. Applicants acknowledge the Examiner's admission that the methods of claims 1-5, 10-12 and 16-21, where the HSV is R7020, and the method of claims 22-23, where the cancer is radiation-resistant epidermal cancer and the HSV is R7020, are enabled.

In response, Applicants traverse the rejection. First, Applicants note that claim 1 has been amended to incorporate the limitations of claims 2 and 11. Second, Applicants direct the Examiner to the application-as-filed, and specifically to Example 2 which discloses that R7020, in addition to effectively reducing tumor volume in a mouse xenograft, was also effective in tumor volume regression of PC-3 prostate cancer adenocarcinoma and hepatoma adenocarcinoma tumor xenografts. Therefore, the application-as-filed provides a sufficiently varied teaching of how to make and use the claimed subject matter to enable the full scope of the claims.

Post-filed art confirms that the application-as-filed provides enabling support for the full scope of the pending claims. Attached as Exhibits A-G are post-filed references disclosing a wide range of tumor types amenable to treatment with HSV.

Exhibit A is a publication by Gutermann *et al.* (Human Gene Therapy 17: 1241-1253, 2006) demonstrating that the combination of HSV NV1020 treatment and

chemotherapy (5-fluorouracil (5-FU), SN38 or Oxaliplatin) shows additive to synergistic cytotoxic effects on colon carcinoma cell lines *in vitro*. In addition, the data demonstrated that the antitumoral activity of NV1020 in combination with 5-FU *in vivo* was superior to single therapy in a mouse model, as measured by a reduction in mean tumor volume. NV1020 is a derivative of R7020 with deletions of U_L24 and the thymidine kinase gene (tk), a deletion of one of two copies of the $\gamma_1 34.5$ gene and a 15-kb deletion over the region jointly shared by the unique short (U_S) and unique long (U_L) regions. A 5.2-kb fragment of HSV-2 DNA containing a tk gene is present, ensuring susceptibility to antiviral chemotherapy.

Exhibit B is a publication by Bennett *et al.* (Cancer Gene Therapy 9: 935-945, 2002) demonstrating superior survival of mice treated with HSV NV1020 compared to HSV G207 in a model of gastric cancer. The authors state that "[t]hus, at lower doses, in particularly resistant tumors, or when therapy is directed at bulky tumors, NV1020 appears superior." (Page 943, second column, last sentence of full paragraph.) G207 is an attenuated recombinant HSV harboring a deletion of both $\gamma 1$ 34.5 genes and inactivation of ICP6 (ribonucleotide reductase (rr)).

Exhibit C is a publication by Cozzi *et al.* (The FASEB Journal 15(7): 1306-8, 2001). Cozzi *et al.* demonstrated a selective, tumor-specific cytolytic effect following intravesical administration of both HSV G207 and HSV NV1020 in an orthotopic mouse model of bladder cancer. The authors go on to state that the viruses appear to be safe in the best available immunocompetent animal model of human bladder cancer currently available (second to last paragraph of discussion).

Exhibit D is a publication by McAuliffe *et al.* (J. Gastrointest. Surg. 4: 580-588, 2000). The authors demonstrated that the use of HSV NV1020 or HSV G207 reduced pancreatic tumor burden in a mouse model.

Exhibit E and **Exhibit F** are published abstracts by Reid *et al.* (The American Society of Clinical Oncology (ASCO), 2009 Gastrointestinal Cancers Symposium, Abstract Number 338) and Geevhargese *et al.* (The American Society of Clinical Oncology (ASCO), 2009 Gastrointestinal Cancers Symposium, Abstract Number 4089). Reid *et al.* and Geevhargese *et al.* reported results of an initial Phase II study using HSV NV1020

administered repeatedly via hepatic artery infusion prior to second line chemotherapy in patients with colorectal adenocarcinoma metastatic to the liver. Their results showed that NV1020 stabilizes liver metastases in highly advanced, refractory metastatic colorectal cancer and may sensitize tumors to salvage chemotherapy and extend survival.

Exhibit G is a publication by Adusumilli *et al.* (The Journal of Gene Medicine 8: 603-615, 2006). Adusumilli *et al.* disclose mesothelioma as a chemoresistant malignancy (page 604, second sentence) and further that "[p]leural mesothelioma is a diffuse disease. Therefore, radiation therapy must include the entire hemithorax and the dose of radiation required to produce local control of the disease is high" (sentences spanning pages 603-604). Further, the first sentence on page 609 states that "[m]alignant mesothelioma cells were relatively resistant to radiation therapy." At page 613, the authors go on to state that "[b]oth viral replication and cytotoxicity of HSV NV1020 and HSV NV1066 were greater than G207 for all cell lines." NV1066, like NV1020 and R7020, expresses a single active copy of $\gamma_1$34.5.

Applicants assert that the collective disclosures of Exhibits A-G, as well as the application-as-filed, demonstrate the wide range of tumors amenable to HSV treatment, and there is no reasonable basis to believe that other tumor types would behave differently. One of ordinary skill in the art would be taught by the specification-as-filed to use a modified HSV (*e.g.*, HSV R7020) in a method for reducing a non-central nervous system tumor mass, including those tumors resistant to conventional therapies.

Beyond the preceding argument, Applicants demonstrate below that the Wands factors confirm that the application-as-filed enables the full scope of the amended claims.

A. The Nature of the Invention

The Examiner characterized the presently claimed subject matter as unpredictable based on its biological nature, citing *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F. 3d 1316, 1330 (Fed. Cir. 2001). The instant claims do not embrace any plant-based subject matter; rather, the claims are drawn to methods for reducing a non-central nervous

system tumor mass comprising the step of administering to a patient suffering from cancer a therapeutically effective amount of a modified Herpes simplex virus (HSV). Thus, the nature of the invention is a medical treatment to reduce tumor mass. Any unpredictability relevant to the "biological" nature of the invention relates to difficulty in identifying useful therapeutics, most of which are effective against a wide range of tumors. Where, as here, the selective cytotoxicity of the modified HSV against tumors has been shown, one of skill would confidently predict such activity would be seen against a wide range of tumors.

B. The Breadth of the Claims

The Examiner has asserted that the claims are broad with respect to the genus of HSVs that can be used in the claimed methods. Specifically, the Examiner asserted that the claims encompass the use of any HSV comprising a modification of an inverted repeat region such that only one $\gamma_1$34.5 gene expresses an active gene product.

Applicants first submit that the amendment to claim 1 renders moot the Examiner's basis for rejection. Specifically, the incorporation of the limitations of claims 2 and 11 further define the modified HSVs that can be used to practice the invention.

In addition, Applicants assert that the breadth of the claims is not overbroad because the claims have been limited to biological therapeutics, more particularly viral therapeutics, more particularly HSV therapeutics, and more particularly HSV with a modified inverted repeat. Thus, the claims are not drawn to all chemical compounds and biological materials, nor even to just all biological materials; rather, the claims are drawn to uses of a particular virus, *i.e.*, HSV, and further to particular modifications of that virus, i.e., modified inverted repeats such that the HSV expresses one active $\gamma_1$34.5 gene.

With respect to the range of radiation-resistant cancers, the Examiner admitted that there is no prior art (page 6 of the Office Action) and Applicants submit that the claims are tailored to the inventors' contribution to the art, i.e., the treatment of any radiation-resistant tumor and not just one or more particular radition-resistant tumor types.

For the foregoing reasons, Applicants submit that the breadth of the amended claims is co-extensive with the scope of the invention. Accordingly, the claims are neither

overbroad nor excessively narrow, and the "breadth of claims" factor favors a finding of enablement commensurate in scope to the claims.

C. The State of the Prior Art and the Unpredictability of the Claimed Invention

The Applicants acknowledge the Examiner's statements that the prior art of record does not teach reducing the mass of a non-central nervous system tumor using any HSV that has only one functional $\gamma_1$34.5 gene wherein the HSV is safe for administration to a patient, nor does it teach treating radiation-resistant tumors using the HSV. The Examiner asserts, however, that the claims are very broad with respect to the number of different HSVs encompassed by the claims as well as the types of radiation-resistant tumors encompassed by claims 22 and 23. The Examiner concludes that the prior art provides little or no guidance for using any of the claim-recited HSVs for treating tumors, and thus there is a relatively incomplete understanding of the field of the broadly claimed invention.

In response, Applicants submit that the Examiner is applying an improper standard. Applicants are claiming new and non-obvious subject matter as their invention. It is unsurprising that the prior art alone provides insufficient guidance. The state of the art, however, is well-developed in providing guidance for growing, modifying and using viruses such as HSV, in assaying for the effect of such viruses on tumor tissue, in obtaining and identifying such tumor tissue, and in treating tumor tissue, both radiation-resistant and radiation-sensitive, for example in humans. Coupled with the guidance in the application-as-filed that the claim-recited modifications of HSV yield selectively cytotoxic therapeutics having the efficacy and safety profiles of desirable therapeutics leads to the conclusion that the state of the art, which is highly developed, and the extensive guidance provided by the application-as-filed in view of the knowledge in the art both favor a finding of enabling support commensurate in scope with the pending claims.

D. Working Examples and Guidance in the Specification

The Examiner asserted that the specification only disclosed that HSV R7020 was effective for treating radiation-resistant epidermal tumor cells (*i.e.*, SQ-206 cells) as well as prostate adenocarcinoma and hepatoma adenocarcinoma cells.

In response, Applicants refer the Examiner to the discussion of guidance in the immediately preceding section of this response. In particular, it is noted that the specification exemplifies the treatment of at least *three* tumor cell types. Applicants assert that the number of working examples coupled with the guidance in the specification also favors a finding of enablement commensurate in scope to the claims.

E. Quantity of Experimentation

The Examiner asserted that additional experimentation would be required in order to practice the full scope of the claims, and that the amount of additional experimentation would be "enormous" and would amount to trial-and-error experimentation to determine which HSVs encompassed by the claims would be effective in the claimed methods and which ones would not. Further experimentation would assertedly be required to determine which radiation-resistant tumors could be effectively treated with the HSVs. Finally, the Examiner asserted that given the relatively incomplete understanding in the field, the elucidation of the HSVs that would be effective in the claimed methods would amount to a significant advancement in the state of the art.

In response, Applicants submit that the Examiner's characterization of the amount of additional experimentation required as "enormous" is a subjective conclusory statement without any reasoned basis. In particular, the specification teaches that the HSVs must have a modified internal repeat such that no more than one $\gamma_1$34.5 gene is expressed. HSVs that differ in areas outside the modified internal repeat, *i.e.*, modifications in non-essential regions of HSV from the perspective of the claimed subject matter, would be expected to be useful therapeutics according to the claims, and the Examiner has not provided evidence or scientific reasons to fairly challenge that position. Conversely, HSV lacking a modified inverted repeat resulting in at most one $\gamma_1$34.5 gene being actively expressed, would be expected to fall outside the claims as lacking the desired selective cytotoxicity. Thus, the therapeutics fall into two groups, not an enormous number. The Examiner has not supported the position that one of skill would be unpersuaded by the working examples showing anti-tumor cell activity of an HSV modified as recited in the claims. One of skill in the art, versed in the science of virology and oncology, would not accept that these fields weren't sciences,

but rather plodding fields of endeavor endlessly engaged in the iterative process of trying each new modified HSV with no expectation of useful activity.

Moreover, even if an "enormous" number of experiments could fairly be envisaged, the case law has established that experimental magnitude alone is not dispositive on the issue of enabling support. See, for example, the number of hybridomas screened in the technology at issue in *In re Wands*, a seminal case in enablement law.

Additionally, Applicants disagree with the Examiner's assertion that elucidating the HSVs effective in tumor mass reductions would amount to a significant advance in the state of the art. The statement is confusing. If the Examiner is asserting that the use of modified HSV to reduce tumor mass has not been demonstrated, the statement is flatly contradicted by the working examples in the application-as-filed. If the Examiner is asserting that selection inventions might be developed that the pending claims would dominate, the point is both irrelevant to the patentability of the pending claims and speculative.

Finally, Applicants have amended the claims to more precisely define the HSV modification. In particular, the limitations of claims 2 and 11 were incorporated into claim 1 to further limit the modified HSV such that only one copy of each of ICP0, ICP4, ORFO, ORFP (rather than only $\gamma_1$34.5) expresses an active gene product, and further comprising deletions of U_L24 and U_L56.

Thus, the quantity of experimentation favors, or at the very least does not disfavor, a finding of enablement commensurate in scope to the claims.

F. Level of Skill in the Art

Applicants acknowledge the Examiner's characterization of the level of skill in the art as high, providing yet another factor supportive of a finding of enablement commensurate in scope to the claims.

G. Conclusion

Applicants have provided dispositive argument that, in view of the present amendments and exemplification of successfully treating not one but three tumor cell types, including a radiation-resistant cell type, the application-as-filed provided enabling support commensurate in scope to the amended claims. Applicants have confirmed this position by demonstrating that a consideration of each of the Wands factors leads to the same conclusion.

Claim Objection

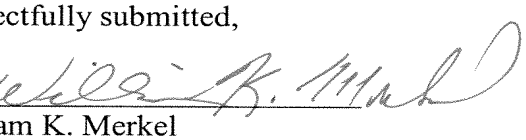
The Examiner objected to claim 13 for being dependent upon a rejected base claim and advised that it would be allowable if rewritten in independent form, including all of the limitations of the base claim and any intervening claims.

Applicants submit that the amendments to independent claim 1 and amendments to claims intervening between claims 13 and claim 1 renders the claim objection moot and it should be withdrawn.

In view of the above amendment and remarks, Applicants submit that the pending claims are in condition for allowance.

Dated: September 14, 2009

Respectfully submitted,

By 

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